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54 **Liquid perfluorocarbons, for use in ocular therapy, and preparations containing them.**

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Description

Ophthalmic preparations are administered into the eye for treating a wide variety of ocular disorders. Usually, these preparations are sterile products designed for either topical application onto the internal eyelid or instillation into the cul-de-sacs strategically positioned between the eyeball (cornea and bulba conjunctiva) and eyelids (palpebral conjunctiva). Ophthalmic preparations may also be prepared in the form of an injection. At the present time, the following are the most common methods of delivering therapeutic substance to the eye: by the mechanism of some sort of vehicle or delivery system to the surface of the eye comprising ocular solutions, suspensions, ointments, gels and inserts; and by either periocular or systemic injections. If there are any diseases within the eye to be treated pharmaceutically, however, the obviously safe and most preferred method of providing that treatment would be by extraocular topical application. Some ophthalmic disorders require the replacement or augmentation of the tear film layer which may be deficient either quantitatively or qualitatively. A topical agent which would provide lubrication and protection to the external surfaces of the eye is required in these disorders. Such disorders include dry eyes syndrome caused by keratoconjunctivitis sica, tear abnormalities, atrophy of the lacrimal gland, ocular pemphigoid, chemical burns, chronic keratoconjunctivitis, corneal epithelium diseases (corneal ulcers, recurrent corneal erosion and marginal ulcers), and corneal vascularization due to corneal injury, infection or transplantation.

Notwithstanding the safety and apparent convenience of topical ophthalmic preparations, several have significant disadvantages which adversely affect their efficiency and efficacy. Some of the disadvantages are inadequate persistence or retention in the cul-de-sacs, irritation, burning or stinging sensations, stickiness, and discomfort, all of which can be attributed to the vehicle, preservatives or drug itself. Because of these disadvantages, patients may not even comply with their doctor's advice for using them.

Presently, all ophthalmic preparations, including those commonly referred to as "eye drops", are required to be sterile before their instillation into the eye. In most ophthalmic preparations, sterility is achieved or maintained by incorporating preservatives. Some preservatives, however, are known to adversely affect the surface structure of the corneal epithelium and disrupt the microvilli which are necessary for the cornea to retain the tear film layer. Thus, the mucin layer of the tear film cannot be properly adsorbed onto the abnormal microvilli of the corneal and conjunctiva surfaces. Without adsorption of the mucin layer onto the corneal and conjunctiva surfaces, the wetting of these surfaces by aqueous tear film layer is hindered. Accordingly, irritation and discomfort result.

In addition to the sterility requirement, eye drops, comprising suspensions and solutions, are rapidly eliminated from the cul-de-sacs by the naso-lacrimal drainage system. As a result of their aqueous properties and low specific gravity, drops are miscible with the secretory liquids of the eye subjecting them to a faster rate of expulsion by way of the blinking mechanism. Unfortunately, their persistence in the cul-de-sacs is limited thereby significantly compromising efficiency and efficacy. Thus, to achieve therapeutic results, ophthalmic eye drops require frequent administration. Because of the physical properties of suspensions, they tend to remain longer in the cul-de-sacs than solutions. Nevertheless, particles are dispersed throughout suspensions which can be irritating to the corneal and conjunctiva surfaces and frequent administration is still required.

Ophthalmic ointments and gels also cause undesirable effects when applied to the internal eyelid. Upon application, they produce a film over the corneal and conjunctiva surfaces blurring vision while usually failing to deliver a uniform dose. Moreover, they may interfere with the precocular tear film precluding its attachment to the corneal and conjunctiva surfaces. Periocular and systemic injections require an ophthalmologist not only to administer but to monitor the drug. Injections tend to cause the patient a great deal of pain and discomfort, anxiety, and inconvenience. Eye inserts provide a delivery system that maintains a low but uniform and constant delivery of a drug. Since the drug is delivered for the duration, frequent administration, as with drops, is not necessary. The major disadvantages associated with ocular inserts involve unnoticed loss of the insert from the eye, slippage of the insert into the area of sight, rupturing of the insert's membrane subjecting the delicate structures of the eye to excessive medication, possible tachyphylaxis, and structural changes in the ciliary muscle resulting from the constant exposure to the drug. Furthermore, there is some degree of manual dexterity required of the patient to position the insert therapeutically and strategically correct.

In contact lens wear, injury to the corneal epithelium may evolve as a direct consequence from the juxtaposition of the contact lens with the corneal surface. Because contact lenses are required to be durable and transparent, the materials presently available for their manufacture are somewhat impermeable to oxygen and carbon dioxide as well as other small molecules. The problems observed with contact lenses manufactured from these materials relates to recurrent corneal edema secondary to suboxidation of the corneal epithelium. That is, when a contact lens is positioned over the cornea, insufficient oxygen will diffuse through it, thereby irritating as well as precluding normal gaseous exchanges of the cornea. The net effect is to cause suboxidation, edema, and irritation resulting in superficial vascularization, and possible opacification of the cornea.

With respect to corneal epithelial disease, e.g., corneal ulcers and marginal corneal ulcers, there is a breakdown of the epithelial barrier which may result in infectious diseases and chronic recurrent breakdowns. The cornea, due to these disorders, will increase in hydration and loss of transparency. Thus,

there is a need for proper ophthalmic preparations that can promote rapid and proper healing of such diseases to avoid formation of corneal scars or opacities. Corneal transplantation or repair is indicated when the cornea has become opaque, infiltrated, or diseased. Because the healing process, as stated above, results in corneal opacification and scars, normal vision can be partially or totally obstructed. In general, corneal transplantation or repair increases hydration while decreasing oxygenation of the cornea. Thus, an ingrowth of vessels is sometimes seen within the cornea after repair or transplantation responding to the corneal scar tissue, increase in hydration and lack of oxygen. Unfortunately, corneal repair or transplantation, as with corneal epithelial disorders, can occlude normal vision when corneal vascularization results.

It is apparent from the above brief overview of various ophthalmic preparations for the eye in pathological processes and the current state of knowledge that there are vital needs for more effective, efficacious and advantageous extraocular ophthalmic preparations.

WO 81/0002 discloses the use of a substantially fluorinated carbon material or a mono- or a di-brominated derivative thereof or a combination thereof or emulsions thereof for the treatment of burn victims.

US—A—3 778 381 and US—A—4 105 798 both disclose the use of perfluorocarbons as the major component in oxygen carriers for use, for instance, as artificial blood or as perfusion materials for the storage of organs such as kidneys prior to transplant.

EP—A—0 089 232, which was published after the filing date of the present Application discloses the use of perfluorocarbon liquids as substitutes for the vitreous or aqueous humours of the eye or as transparentizing agents in the cornea or lens of the eye. It also discloses the use of radio-opaque liquid perfluorocarbons in diagnostic procedures of the eye.

GB—A—2 041 221 discloses the use of a perfluorocarbon containing an organic iodine compound as an X-ray contrast agent for use in angiography.

The present invention provides, in its various aspects, an ophthalmic composition for providing lubrication and protection to the surface of the eye comprising a transparent or light transmissive, stable, inert, viscous perfluorocarbon or substituted derivative thereof and either an ophthalmologically acceptable carrier therefor, provided that the carrier is not substantially only water, or an effective amount of a pharmaceutical agent for treating an extraocular disorder.

The present invention also provides a medicament package comprising a container adapted for the application of its contents topically to the eye, the contents of the container comprising a transparent or light transmissive, stable, inert, viscous perfluorocarbon or substituted derivative thereof.

The present invention also relates to use of a transparent or light transmissive, stable, inert, viscous perfluorocarbon or substituted derivative thereof for the preparation of a medicament for extraocular use in the lubrication, protection or treatment of the surface of the eye.

Liquid perfluorocarbons and substituted derivatives thereof have been found to be useful as a therapeutic agent or vehicle in extraocular ophthalmic preparations. These liquids act as lubricating, wetting or protective agents, as well as vehicles for other substances or drugs. These liquids will also remain within the cul-de-sacs for greater periods of time since they have high specific gravities. In their pure state, these liquids are not aqueous, wherefore isotonicity and pH do not need to be considered. Moreover, since preservatives and materials to regulate isotonicity or pH are not required, or lesser amounts thereof are needed to be incorporated into such liquids, irritation to the eye is minimized. Corneal and conjunctiva surfaces, when treated with such liquids, are provided with greater amounts of oxygen because of the high oxygen diffusion properties of the perfluorocarbons.

This invention is directed to the use of perfluorocarbon liquids and substituted derivatives thereof in extraocular ophthalmologic preparations. Perfluorocarbons have been found to be advantageous agents when instilled within the eye as well as a possible vehicle for other drugs and agents. Perfluorocarbon liquids have been instilled into the eye of an experimental animal as well as a human to function as a lubricant or wetting solution. They have been proven to be useful ophthalmic solutions, and the eyes of experimental animals or humans treated with this liquid maintained normal vision and demonstrated no adverse effects. Furthermore, the high specific gravity of the perfluorocarbon liquids permits their retention within the cul-de-sacs for a greater period of time. These and other remarkable discoveries will become further understood in the details which follow herein below.

The perfluorocarbon liquids preferably employed are transparent or light transmissive, stable, inert, and remain viscous indefinitely. This invention is predicated in part upon the discovery that such perfluorocarbon liquids are ideal in extraocular preparations. Moreover, they dissolve oxygen and carbon dioxide extremely well, and can be sterilized by autoclaving. Thus, these liquids are comprised of unusual chemical and physical properties endowing them with unique, unexpected and advantageous uses in extraocular ophthalmic preparations. Another important discovery involved in this invention is that these perfluorocarbons can be instilled into the cul-de-sacs and will remain therein for greater periods of time because of their greater density and immiscibility with aqueous media. Also, it was found that upon blinking, a microemulsion of the perfluorocarbon liquid is developed within the precocular tear film providing significant lubricating and wetting properties for the corneal and conjunctiva surfaces. Remarkably, these microemulsions remained in contact with the external surfaces of the eye for a

substantial period of time. Finally, the external surface of the eye will be better oxygenated because of the perfluorocarbon's high diffusion properties for oxygen and carbon dioxide.

In another feature of the invention, perfluorocarbon liquids can be ideally employed in contact lens wear, corneal epithelial disease, and corneal transplantation and repair. For instance, the liquids will enhance oxygenation of the cornea and lubricate the epithelial surface to reduce adverse side effects associated with the contact lens use. In addition, the liquids can be applied as a protective agent in corneal epithelial diseases to prevent infection and chronic recurrent epithelial breakdowns. In corneal repair, transplantation or disease, the liquids enhance oxygenation of the corneal tissue and decrease hydration thereby reducing superficial vascularization, scar tissue and opacities.

10

Detailed description of the invention

The suitable perfluorocarbons and any derivatives thereof may be generally termed as "liquids". The term "liquids", as used herein, is a comprehensive designation incorporating compounds that are in a state neither solid nor gaseous such as liquids, emulsions and gels. The term "perfluorocarbon" means a "cyclic" or "acyclic" compound of carbon, whereas the term "substituted derivatives thereof" characterizes substituted perfluorocarbons with chemical elements within their structures such as oxygen, nitrogen and bromine. It should also be noted that the term "perfluorocarbon" denotes substitution of all hydrogen atoms attached to the carbon atom chain or ring and any carbon side groups with fluorine. It is conceivable in the manufacture of such compounds that minor amounts of substantially fluorinated derivatives may be mixed with completely fluorinated compounds. This is permissible providing that the lack of complete replacement of all hydrogens does not affect the essential characteristics of the liquid perfluorocarbons of this invention, particularly when active hydrogens critically enhance the toxicity of the compounds. Among the perfluorocarbon compounds which may be employed are perfluorotributylamine (FC47), perfluorodecalin (PP5), perfluorotetrahydrofuran (FC80), perfluoroether (PID) [(CF₃)₂CFOCF₂(CF₂)₂CF₂OCF(CF₃)₂], perfluoroether (PIID) [(CF₃)₂CFOCF₂(CF₂)₆CF₂OCF(CF₃)₂], perfluoropolymer (E3)



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perfluoropolymer (E4)



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perfluoroetherpolymer (Fomblin Y/01), perfluorododecane, perfluorobicyclo[4.3.0]nonane, perfluoro-trimethylcyclohexane, perfluoroisopropylcyclohexane, perfluoroendotetrahydrodicyclopentadiene, perfluoroadamantane, perfluoroexo - tetrahydrodicyclopentadiene, perfluorobicyclo[5.3.0]decane, perfluoro-tetramethylcyclohexane, perfluoro - 1 - methyl - 4 - isopropylcyclohexane, perfluoro - n - butylcyclohexane, perfluorodimethylbicyclo[3.3.1]nonane, perfluoro - 1 - methyladamantane, perfluoro - 1 - methyl - 4 - t - butylcyclohexane, perfluorodecahydroacenaphthene, perfluoro-trimethylbicyclo[3.3.1]-nonane, perfluoro - n - undecane, perfluorotetradecahydrophenanthrene, perfluoro - 1,3,5,7 - tetramethyladamantane, perfluorododecahydrofluorene, perfluoro - 1,3 - dimethyl adamantane, perfluoro - n - octylcyclohexane, perfluoro - 7 - methyl bicyclo[4.3.0]nonane, perfluoro - p - diisopropylcyclohexane, and perfluoro - m - diisopropylcyclohexane.

It is understood that perfluorocarbon liquids of this invention may be formed of "neat" perfluorocarbon liquids or emulsions, suspensions or solutions of perfluorocarbons in mixture with themselves or other solvents. For instance, perfluoro-1,3-dimethyl adamantane is normally a solid but in mixture with perfluoro-trimethylbicyclo[3.3.1]nonane a liquid is formed, i.e., DAWN. The neat liquids are preferred because of their inertness and non-aqueousness. Also, when the perfluorocarbon liquids are emulsified in water, sometimes milky or even somewhat clear or transparent liquids, emulsions, gels or solutions might result which may be suitable for use in this invention. In extraocular ophthalmic preparations, fluid transparency is preferred, but even somewhat milky fluids may be used. In brief, then, the nature of the "liquid" state may include pure liquid perfluorocarbon, emulsions, solutions or suspensions of perfluorocarbon compounds in other liquid mediums. Suitable emulsions or suspensions of perfluorocarbons for use in this invention are disclosed in U.S. Patent 3,911,138 and 4,105,798.

Perfluorocarbons are capable of being synthesized by well known chemical or electrochemical processes. The chemical processes yield fairly pure substances of known structure, having well defined boiling points, whereas the electrochemical processes tend to yield a mixture of isomers, the liquids having less well defined boiling points. With respect to gas chromatography, the liquid is capable of being well defined by either the packed or capillary column procedure. The standard to define each compound in gas chromatography is prepared as follows: 2 microliters of neat liquid are added to 120 milliliters of air in a sealed bottle and allowed to vaporise producing a stock standard; upon vaporisation, 120 microliters of the

65

vapor from the stock standard are added to another 120 milliliters of air in a sealed bottle producing the working standard; the sample measured by the procedure is withdrawn from the working standard, thus, a typical sample will contain 16.7 pico liters of perfluorocarbon per milliliter of standard; however, in the capillary column procedure, the sample is split into a ratio of 23:1, therefore, only 1/23 of the sample is actually measured. As indicated in Table I, the retention time is highly definitive of the liquid used in this invention. Moreover, the capillary procedure is more specific than the packed column procedure by defining additional characteristic peaks of the compound. Thus, a more precise definition of the compound can be had with the capillary column procedure as exemplified for perfluoro-1-methyldecalin in the following Table.

TABLE I
Gas chromatography*

	Packed column**	Capillary column***
Set Up		
Standard	[16.7 pl/ml]****	[16.7 pl/ml]****
Recorder Sensitivity	0.001v full scale	0.001v full scale
Column Temperature	100°C	37°C
Detector Temperature	250°C	250°C
Injector Temperature	150°C	150°C
M ₂ Gas Flow	40 ml/min	40 ml/min
Split	—	23:1
Recorder Speed	2.5 cm/min	2.5 cm/min
Compound		
PP9		
(perfluoro-1-methyldecalin)		
Attenuation	8	4
Sample	50 µl	100 µl
Peaks	3	7
Retention Time		
Peak ₁	124.8	211.2 s
Peak ₂	136.8 s	240 s
Peak ₃	196.8 s	340.8 s
Peak ₄	—	362.4 s
Peak ₅	—	379.2 s
Peak ₆	—	391.2 s
Peak ₇	—	403.2 s

* Antek 300 Gas Chromatography instrument

** Supelco, Inc. Packed Column

*** Scientific Glass Engineering Capillary Column

**** pl/ml=picoliters/milliliter

Preferred perfluorocarbons, exemplified by perfluoro-1-methyldecalin, all have in common a high solubility for oxygen and carbon dioxide, stability, inertness, high density, and transparency. They are suitable for instillation into the eye as extraocular ophthalmic preparations and in the treatment of ophthalmologic disorders. A particular perfluorocarbon or a mixture of perfluorocarbons falling within the

family of liquids exemplified by the above derivative may be used according to the principles of my invention. One main property generic to the preference of the liquids according to this invention over other fluoro-containing liquids is their chemical structure rendering them RES-phobic. These compounds have been defined in U.S. Patent 3,911,138 as "perfluorocyclocarbons", especially perfluoro (methylcyclohexane), perfluoro-1-methyldecalin [also known as perfluoro(decahydro-1-methylnaphthalene)], perfluoro(1,3-dimethylcyclohexane), perfluoro (decahydronaphthalene), and perfluoro (decahydro-dimethylnaphthalene), or mixtures thereof, perfluorinated bicyclononane, perfluorinated bicyclooctane, perfluorinated adamantane hydrocarbon, perfluoromethyladamantane and perfluorodimethylbicyclo[3.3.1]nonane, perfluorodimethyladamantane and perfluorotrimethylbicyclo-[3.3.1]nonane, perfluorotetrahydrodicyclopentadiene and perfluorobicyclo[5.3.0]decane, perfluorotetrahydrodicyclopentadiene, perfluorinated bicyclononane, perfluorinated bicyclooctane, perfluorinated adamantane hydrocarbon, perfluoromethyladamantane and perfluorodimethylbicyclo[3.3.1]nonane, perfluorodimethyladamantane and perfluorotrimethylbicyclo-[3.3.1]nonane, and perfluorotetrahydrodicyclopentadiene and perfluorobicyclo[5.3.0]decane. RES-phobic perfluorinated liquids tend to accumulate less in the bodies of animals, principally in the liver, and to a lesser extent in the spleen and kidneys. This is significant because such liquids will not become fixed indefinitely within the cells of the organ. There is another property associated with this class of perfluorocarbons that is preferentially utilized when they are introduced into the eye. A perfluorocarbon or a mixture thereof is preferably employed having a vapor pressure within the range of 133 to 3,325 Pa (1 to 25 torr) at about 35°C. Thus, such liquids or mixtures are not only RES-phobic, but upon escaping the cell expediently, they will not cause adverse gas collection in the tissue of animals.

In their broadest application, the liquid perfluorocarbons are instilled into the eye as extraocular ophthalmologic preparations to treat ocular disorders. The liquid can be placed or instilled in the eye by conventional eye droppers such as a dropper bottle, a separate dropper or pipette. Other means necessary to instill a gel or ointment may be used. For example, the neat liquid can be dropped into the interior cul-de-sac, the space between the eyeball and eyelid, by tilting the head back and gently pulling down the inferior palpebral conjunctiva until a "V" pocket is formed between the eye and the inferior eyelid, whereupon the liquid or gel can be instilled into the "V" pocket. The objective is to instill the neat liquid into the inferior fornix of the inferior cul-de-sac. Because of the density, viscosity, and immiscibility of the perfluorocarbons, such liquids will sink to and remain at the inferior fornix. The mechanism of blinking will then act to disperse the liquids across the corneal and conjunctiva surfaces. The liquids, as a direct result of their immiscibility, will usually disperse as microemulsions rather than solutions. Microemulsions will be dispersed within the lipid layer of the precocular tear film acting to lubricate and wet the epithelial surfaces with a substantial amount remaining in the cul-de-sacs for significant periods of time being available for continuous dispersion. The significant retention of the liquids within the cul-de-sacs occurs as a result of their immiscibility, density and viscosity.

The eye utilizes the mechanism of blinking to not only spread the fluids therein, but also to eliminate such fluids by way of the lacrimal canaliculi. That is, the drainage of fluid, such as tears, does not depend upon gravity for its elimination, but rather, the fluid enters the puncta and passes along the lacrimal canaliculi by capillary attraction aided by aspiration caused by a contraction of muscle embedded within the eyelids. When the eyelids are partially closed, as in the initial phase of blinking, contraction of the muscles causes the puncta to close. The canaliculi are then compressed while the lacrimal sac is dilated when the eyelids are further closed. Fluid, thus, is aspirated into the sac and forced down the nasolacrimal duct toward its aperture into the nose. When a perfluorocarbon liquid is dropped into the eye, the mechanism of blinking is less efficient in its elimination. This effect is due to the density, viscosity, and immiscibility of these liquids which act to antagonize the aspiration effect of blinking, retarding their expulsion. Perfluorocarbon liquids, as extraocular ophthalmology preparations, are beneficial for treating dry eyes and tear abnormalities such as aqueous tear deficiency, tear film instability, surfacing problem, and the effects of irritants. Upon dispersion of the perfluorocarbon liquids across the corneal and conjunctiva surfaces, the microemulsions are dispersed within the lipid or outermost layer of the tear film where it will primarily demonstrate its effect. There should be little or no adverse effects on the mucin layer, as seen with ointments, when such liquids are instilled. Thus, the instillation of perfluorocarbon liquids as extraocular ophthalmology preparations will provide a lubricating, wetting or protecting surface without interfering with mucin adsorption onto the corneal and conjunctiva surfaces. Thus, the liquids will not only provide these beneficial effects on the precocular tear film, but will remain within the cul-de-sacs for longer periods of time as a result of their immiscibility, density and viscosity. In contrast to these advantageous liquid perfluorocarbons, the present ocular lubricants, which include solutions of hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinyl pyrrolidone soluble polymers, dextran and mixtures thereof are rapidly cleared from the eye and require frequent administration.

No preservatives are necessary to maintain sterility in the preferred preparations of the invention because neat perfluorocarbons are nonaqueous. Thus, the microvilli within the epithelium of the cornea are not adversely affected, as exhibited by present extraocular ophthalmic preparations, and the adsorption of mucin onto the microvilli remain intact. Since the liquids are nonaqueous, the pH or isotonicity does not have to be considered to avoid irritation and stinging upon their instillation. With contact lenses, the liquids can be employed as protective, wetting, lubricating and oxygenating extraocular

ophthalmic preparations. The irritation and possible superficial vascularization and specification of the cornea will also be reduced. In corneal epithelial diseases, such as corneal ulcers, recurrent corneal erosion and marginal corneal ulcers, the liquid perfluorocarbon preparations will decrease the incidence of corneal vascularization, scarring and opacification as seen with such corneal disorders. Likewise, in corneal repair and transplantation, the application of perfluorocarbon liquids during and after such procedures should decrease or eliminate the untoward side effects of corneal vascularization, scarring and opacification. It is the oxygen-carrying property of the liquid perfluorocarbons as well as their non-aqueous, viscous, and dense properties that make them ideal liquids to treat such procedures.

Due to the retention of perfluorocarbon liquids within the eye for considerable periods of time, such liquids can be employed as suitable vehicles for other substances. Presently drops, ointments, and ocular inserts are utilized to deliver drugs extraocularly. As stated above, solutions and suspensions are readily excreted, the preparations available may contain irritants, ointments blur vision and interfere with mucin adsorption, while ocular inserts are uncomfortable and subject to rupture or loss. With the use of liquid perfluorocarbons as vehicles, the number of administrations can be reduced while the adverse effects of ointments, suspensions and inserts are eliminated.

In view of the above description, it is apparent that perfluorocarbon liquids and derivatives thereof are unique and advantageous liquids when used in extraocular ophthalmological preparations. The invention, its principles and objectives will be further understood in view of the following examples with reference to the drawings which are anatomical illustrations of the eye. Fig. 1 constitutes a vertical section of the eye illustrating the eyelid, and the external and internal components of the eye. As stated, the secretory components of the eye secrete the precocular tear film which is comprised of three layers. The oil layer originates from the meibomian glands and glands of Zeis, the aqueous layer is produced by the lacrimal and accessory lacrimal (Wolfring's and Krause) glands, while mucin is made by the goblet cells (not illustrated) which are scattered over the palpebral conjunctiva. The superior and inferior fornix constitute the deposit area within the superior and inferior cul-de-sacs. The middle layer, the tear fluid, is aqueous and provides hydration, antibacterial agents and nutritional elements to the external surfaces. The innermost layer of the tear film comprises mucin which covers the conjunctiva and corneal surfaces. Mucin function to permit the overlying aqueous layer to spread across the surfaces. Herein the term "external surface" of the eye is meant to include broadly all such surfaces shown in the drawing and referred to herein which may come into direct contact with liquid which is introduced between an eyelid and eyeball.

Fig. 2 illustrates the excretory apparatus employed by the eye to eliminate fluids therein. The puncta are the apertures leading into the lacrimal canaliculus and eventually into the nasal lacrimal duct.

Example I

A single drop from a 3 ml syringe and a 25 gauge needle containing perfluoro 1-methyldecalin (PP9) was instilled, i.e. placed into each eye of a rabbit. The rabbit was observed for a period of two hours through a Codman-Mentor Operating Microscope. Specifically, the examination of the rabbit cornea showed no evidence of corneal toxicity as manifested by the lack of epithelial staining the maintenance of corneal transparency. Also, there was no inflammation or irritation observed in the bulbar or palpebral conjunctiva. Further, the rabbit demonstrated no abnormal visual responses.

Example II

A single drop containing perfluoro-1-methyldecalin (PP9), was instilled into the right eye of a human. The instillation, using a plastic dropper bottle, was made onto the interior cul-de-sac of the right eye. Prior to and after instilling the liquid, various tests including Visual Acuity, Corneal Sensitivity, Anterior Segment Examination with and without Fluorescein, Rose Bengal and Tear Film stability were conducted for comparative purposes. No negative effects or results were found before or after the instillation of the perfluoro-1-methyldecalin. Thus, the results demonstrated that the eye remained unchanged after the experiment. The subject's visual acuity, as measured before and after, was 20/20 corrected. There was no change in his corneal sensitivity. The slit-lamp biomicroscopy test with and without fluorescein and with and without Rose Bengal detected no corneal ulcers, irritations or drying cells on his ocular surface. The subject's tear stability or break-up time, also measured before and after, remained the same at 25 seconds. Furthermore, the subject experienced no gritty, stinging, or burning sensations, or excess mucous secretions from the instilled liquid. The subject found the liquid to be comfortable, soothing and did not interfere with his blinking or vision. The liquid was detected in his eye for up to an hour after it had been instilled. Finally, there were no ocular, nasal, or gastrointestinal side effects experienced by the subject.

In view of the above detailed description and examples, other modifications will become apparent to those of ordinary skill in the art to which this invention pertains.

60 Claims

1. An ophthalmic composition for providing lubrication and protection to the surface of the eye comprising a transparent or light transmissive, stable, inert, viscous perfluorocarbon or substituted derivative thereof and an ophthalmologically acceptable carrier therefor, provided that the carrier is not substantially only water.

2. The composition of Claim 1, wherein the ophthalmologically acceptable carrier is a gel or ointment.
3. The composition of Claim 1 or Claim 2, wherein the perfluorocarbon is a perfluorocyclocarbon.
4. The composition of Claim 3, wherein the perfluorocyclocarbon is perfluoro (methylcyclohexane),
perfluoro (1,3-dimethylcyclohexane), perfluoro (decahydronaphthalene), perfluoro-(decahydro-1-methyl-
5 naphthalene), perfluoro (decahydrodimethylnaphthalene), perfluorodimethyladamantane, perfluoro-
trimethylbicyclo[3.3.1]nonane, perfluorotetrahydrodicyclopentadiene, perfluorobicyclo[5.3.0]decane,
perfluorodimethylbicyclo[3.3.1]nonane, or a mixture thereof.
5. The composition of Claim 4, wherein the perfluorocyclocarbon is perfluoro-1-methyl decalin.
6. An ophthalmic composition for providing lubrication and protection to the surface of the eye
10 comprising a transparent or light transmissive, stable, inert, viscous perfluorocarbon or substituted
derivative thereof and an effective amount of a pharmaceutical agent for treating an extraocular disorder.
7. The composition of Claim 6, further including an ophthalmologically acceptable carrier.
8. The composition of Claim 7, wherein the ophthalmologically acceptable carrier is a gel or ointment.
9. The composition of any one of Claims 6 to 8, wherein the perfluorocarbon is a perfluorocyclocarbon.
- 15 10. The composition of Claim 9, wherein the perfluorocyclocarbon is perfluoro (methylcyclohexane),
perfluoro(1,3-dimethylcyclohexane), perfluoro(decahydronaphthalene), perfluoro-(decahydro-1-methyl-
naphthalene), perfluoro(decahydrodimethylnaphthalene), perfluorodimethyladamantane, perfluoro-
trimethylbicyclo[3.3.1]nonane, perfluorotetrahydrodicyclopentadiene, perfluorobicyclo[5.3.0]decane, per-
fluorodimethylbicyclo[3.3.1]nonane, or a mixture thereof.
- 20 11. The composition of Claim 10, wherein the perfluorocyclocarbon is perfluoro-1-methyl decalin.
12. A medicament package comprising a container adapted for the application of its contents topically
to the eye, the contents of the container comprising a transparent or light transmissive, stable, inert,
viscous perfluorocarbon or substituted derivative thereof.
13. The medicament package of Claim 12 wherein the container comprises an eye dropper.
- 25 14. The medicament package of Claim 12 or Claim 13, wherein the contents of the container further
comprises a pharmaceutical agent for treating an extraocular disorder.
15. The medicament package of any one of Claims 12 to 14, wherein the contents of the container
further comprises an ophthalmologically acceptable carrier.
16. The medicament package of Claim 15, wherein the ophthalmologically acceptable carrier is a gel or
30 ointment.
17. The medicament package of any one of Claims 12 to 16, wherein the perfluorocarbon is a
perfluorocyclocarbon.
18. The medicament package of Claim 17, wherein the perfluorocyclocarbon is perfluoro(methylcyclo-
hexane), perfluoro(1,3-dimethylcyclohexane), perfluoro(decahydronaphthalene), perfluoro-(deca-
35 hydro-1-methylnaphthalene), perfluoro(decahydrodimethylnaphthalene), perfluorodimethyladamantane,
perfluorotrimethylbicyclo[3.3.1]nonane, perfluorotetrahydrodicyclopentadiene, perfluorobicyclo[5.3.0]-
decane, perfluorodimethylbicyclo[3.3.1]nonane, or a mixture thereof.
19. The medicament package of Claim 18, wherein the perfluorocyclocarbon is perfluoro-1-methyl
decalin.
- 40 20. Use of a transparent or light transmissive, stable, inert, viscous perfluorocarbon or substituted
derivative thereof for the preparation of a medicament for extraocular use in the lubrication, protection or
treatment of the surface of the eye.
21. The use of Claim 20, wherein the perfluorocarbon is a perfluorocyclocarbon.
22. The use of Claim 21, wherein the perfluorocyclocarbon is perfluoro(methylcyclohexane),
45 perfluoro(1,3-dimethylcyclohexane), perfluoro(decahydronaphthalene), perfluoro-(decahydro-1-methyl-
naphthalene), perfluoro(decahydrodimethylnaphthalene), perfluorodimethyladamantane, perfluoro-
trimethylbicyclo[3.3.1]nonane, perfluorotetrahydrodicyclopentadiene, perfluorobicyclo[5.3.0]decane,
perfluorodimethylbicyclo[3.3.1]nonane, or a mixture thereof.
23. The use of Claim 22, wherein the perfluorocyclocarbon is perfluoro-1-methyl decalin.

Patentansprüche

1. Ophthalmologische Zusammensetzung zum Schmieren und Schutz der Oberfläche des Auges,
dadurch gekennzeichnet, daß sie einen transparenten oder lichtdurchlässigen, stabilen, inerten, viskosen
55 Perfluorkohlenstoff oder ein substituiertes Derivat davon und einen ophthalmologisch annehmbaren
Träger dafür enthält, mit der Maßgabe, daß der Träger im wesentlichen nicht nur Wasser ist.
2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß der ophthalmologisch annehm-
bare Träger ein Gel oder eine Salbe ist.
3. Zusammensetzung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß der Perfluorkohlenstoff
60 ein Perfluorocyclokohlenstoff ist.
4. Zusammensetzung nach Anspruch 3, dadurch gekennzeichnet, daß der Perfluorocyclokohlenstoff
Perfluor(methylcyclohexan), Perfluor(1,3-dimethylcyclohexan), Perfluor(decahydronaphthalin), Perfluor-
(decahydro-1-methyl-naphthalin), Perfluor(decahydrodimethylnaphthalin), Perfluordimethyladamantan,
Perfluorotrimethylbicyclo[3.3.1]nonan, Perfluortetrahydrodicyclopentadien, Perfluorbicyclo[3.3.0]decan,
65 Perfluordimethylbicyclo[3.3.1]nonan, oder eine Mischung davon ist.

5. Zusammensetzung nach Anspruch 4, dadurch gekennzeichnet, daß der Perfluorocyclokohlenstoff Perfluor-1-methyl-decalin ist.
6. Ophthalmologische Zusammensetzung zum Schmieren und Schutz der Oberfläche des Auges, dadurch gekennzeichnet, daß sie einen transparenten oder lichtdurchlässigen, stabilen, inerten, viskosen
- 5 Perfluorkohlenstoff oder ein substituiertes Derivat davon und eine wirksame Menge eines pharmazeutischen Mittels zur Behandlung einer Krankheit des äußeren Auges enthält.
7. Zusammensetzung nach Anspruch 6, dadurch gekennzeichnet, daß sie weiters einen ophthalmologisch annehmbaren Träger enthält.
8. Zusammensetzung nach Anspruch 7, dadurch gekennzeichnet, daß der ophthalmologisch annehmbare Träger ein Gel oder eine Salbe ist.
- 10 9. Zusammensetzung nach einem der Ansprüche 6 bis 8, dadurch gekennzeichnet, daß der Perfluorkohlenstoff ein Perfluorocyclokohlenstoff ist.
10. Zusammensetzung nach Anspruch 9, dadurch gekennzeichnet, daß der Perfluorocyclokohlenstoff Perfluor(methylcyclohexan), Perfluor(1,3-dimethylcyclohexan), Perfluor(decahydronaphthalin),
- 15 Perfluor(decahydro-1-methyl-naphthalin), Perfluor(decahydrodimethylnaphthalin), Perfluordimethyladamantan, Perfluortrimethylbicyclo[3.3.1]nonan, Perfluortetrahydrodicyclopentadien, Perfluorbicyclo[5.3.0]decan, Perfluordimethylbicyclo[3.3.1]nonan, oder eine Mischung davon ist.
11. Zusammensetzung nach Anspruch 10, dadurch gekennzeichnet, daß der Perfluorocyclokohlenstoff Perfluor-1-methyl-decalin ist.
- 20 12. Arzneimittelpackung mit einem für die topische Applikation seines Inhalts auf das Auge geeigneten Behälter, dadurch gekennzeichnet, daß der Inhalt des Behälters einen transparenten oder lichtdurchlässigen, stabilen, inerten, viskosen Perfluorkohlenstoff oder ein substituiertes Derivat davon enthält.
13. Arzneimittelpackung nach Anspruch 12, dadurch gekennzeichnet, daß der Behälter einen Augentropfer umfaßt.
- 25 14. Arzneimittelpackung nach Anspruch 12 oder 13, dadurch gekennzeichnet, daß der Inhalt des Behälters weiters ein pharmazeutisches Mittel zur Behandlung einer Krankheit des äußeren Auges enthält.
15. Arzneimittelpackung nach einem der Ansprüche 12 bis 14, dadurch gekennzeichnet, daß der Inhalt des Behälters weiters einen ophthalmologisch annehmbaren Träger enthält.
16. Arzneimittelpackung nach Anspruch 15, dadurch gekennzeichnet, daß der ophthalmologisch
- 30 annehmbare Träger ein Gel oder eine Salbe ist.
17. Arzneimittelpackung nach einem der Ansprüche 12 bis 16, dadurch gekennzeichnet, daß der Perfluorkohlenstoff ein Perfluorocyclokohlenstoff ist.
18. Arzneimittelpackung nach Anspruch 17, dadurch gekennzeichnet, daß der Perfluorocyclokohlenstoff Perfluor(methylcyclohexan), Perfluor(1,3-dimethylcyclohexan), Perfluor(decahydronaphthalin),
- 35 Perfluor(decahydro-1-methyl-naphthalin), Perfluor(decahydrodimethylnaphthalin), Perfluordimethyladamantan, Perfluortrimethylbicyclo[3.3.1]nonan, Perfluortetrahydrodicyclopentadien, Perfluorbicyclo[5.3.0]decan, Perfluordimethylbicyclo[3.3.1]nonan, oder eine Mischung davon ist.
19. Arzneimittelpackung nach Anspruch 18, dadurch gekennzeichnet, daß der Perfluorocyclokohlenstoff Perfluor-1-methyl-decalin ist.
- 40 20. Verwendung eines transparenten oder lichtdurchlässigen, stabilen, inerten, viskosen Perfluorkohlenstoffs oder eines substituierten Derivates davon zur Herstellung eines Arzneimittels zur extraokularen Verwendung zum Schmieren, Schutz oder zur Behandlung der Augenoberfläche.
21. Verwendung nach Anspruch 20, dadurch gekennzeichnet, daß der Perfluorkohlenstoff ein Perfluorocyclokohlenstoff ist.
- 45 22. Verwendung nach Anspruch 21, dadurch gekennzeichnet, daß der Perfluorocyclokohlenstoff Perfluor(methylcyclohexan), Perfluor(1,3-dimethylcyclohexan), Perfluor(decahydronaphthalin), Perfluor(decahydro-1-methyl-naphthalin), Perfluor(decahydrodimethylnaphthalin), Perfluordimethyladamantan, Perfluortrimethylbicyclo[3.3.1]nonan, Perfluortetrahydrodicyclopentadien, Perfluorbicyclo[5.3.0]decan, Perfluordimethylbicyclo[3.3.1]nonan, oder eine Mischung davon ist.
- 50 23. Verwendung nach Anspruch 22, dadurch gekennzeichnet, daß der Perfluorocyclokohlenstoff Perfluor-1-methyl-decalin ist.

Revendications

- 55 1. Composition ophtalmique pour assurer une lubrification et de la protection à la surface de l'oeil, comprenant un perfluorocarbure visqueux, inerte, stable, transparent ou pouvant transmettre la lumière ou un dérivé de substitution de celui-ci et un support ophtalmologiquement acceptable à la condition que le support ou véhicule ne soit pas constitué essentiellement par de l'eau seule.
2. Composition selon la revendication 1, dans laquelle le support ophtalmologiquement acceptable est
- 60 un gel ou un onguent.
3. Composition selon la revendication 1 ou la revendication 2, dans laquelle le perfluorocarbure est un perfluorocyclocarbure.
4. Composition selon la revendication 3, dans laquelle le perfluorocyclocarbure est du
- 65 perfluoro-(méthylcyclohexane), du perfluoro-(1,3-diméthylcyclohexane), du perfluoro-(décahydro-naphtalène), du perfluoro-(décahydro-1-méthyl-naphtalène), du perfluoro-(décahydrodiméthyl-

naphthalène), du perfluorodiméthyladamantane, du perfluoro-triméthylbicyclo[3.3.1]nonane, du perfluoro-tétrahydrodicyclopentadiène, du perfluorodicyclo[3.3.0]décane, du perfluorodiméthylbicyclo[3.3.1]nonane, ou un de leurs mélanges.

5 5. Composition selon la revendication 4, dans laquelle le perfluorocyclocarbure est de la perfluoro-1-méthyldecaline.

6. Composition ophtalmique destinée à assurer la lubrification et la protection de la surface de l'oeil, comprenant un perfluorocarbure visqueux, inerte, stable, transparent ou capable de transmettre la lumière ou un dérivé de substitution de celui-ci et une quantité efficace d'un agent pharmaceutique destiné à traiter un trouble extra-oculaire.

10 7. Composition selon la revendication 6, comprenant en outre un support ophtalmologiquement acceptable.

8. Composition selon la revendication 7, dans laquelle le support ophtalmologiquement acceptable est un gel ou un onguent.

9. Composition selon l'une quelconque des revendications 6 à 8, dans laquelle le perfluorocarbure est
15 un perfluorocyclocarbure.

10. Composition selon la revendication 9, dans laquelle le perfluorocyclocarbure est du perfluoro-(méthylcyclohexane), du perfluoro-(1,3-diméthylcyclohexane), du perfluoro-(décahydro-naphthalène), du perfluoro-(décahydro-1-méthyl-naphthalène), du perfluoro-(décahydrodiméthyl-naphthalène), du perfluorodiméthyladamantane, du perfluoro-triméthylbicyclo[3.3.1]nonane, du perfluorotétrahydro-
20 cyclopentadiène, du perfluorodicyclo[5.3.0]décane, du perfluorodiméthylbicyclo[3.3.1]nonane, ou un de leurs mélanges.

11. Composition selon la revendication 10, dans laquelle le perfluorocyclocarbure est de la perfluoro-1-méthyldecaline.

12. Trousse à médicaments comprenant un récipient destiné à l'application topique de son contenu à
25 l'oeil, le contenu du récipient comprenant un perfluorocarbure visqueux, inerte, stable, transparent ou capable de transmettre la lumière ou un dérivé de substitution de ce perfluorocarbure.

13. Trousse de médicaments selon la revendication 12, dans laquelle le récipient comprend un compte-gouttes pour les yeux.

14. Trousse à médicaments selon la revendication 12 ou la revendication 13, dans laquelle le contenu
30 du récipient comprend en outre un agent pharmaceutique destiné à traiter un trouble extra-oculaire.

15. Trousse à médicaments selon l'une quelconque des revendications 12 à 14, dans laquelle le contenu du récipient contient en outre un support ophtalmologiquement acceptable.

16. Trousse à médicaments selon la revendication 15, dans laquelle le support pharmacologiquement acceptable est un gel ou onguent.

17. Trousse à médicaments selon l'une quelconque des revendications 12 à 16, dans laquelle le
35 perfluorocarbure est un perfluorocyclocarbure.

18. Trousse à médicaments selon la revendication 17, dans laquelle le perfluorocyclocarbure est du perfluoro-(méthylcyclohexane), du perfluoro-(1,3-diméthylcyclohexane), du perfluoro-(décahydro-naphthalène), du perfluoro-(décahydro-1-méthyl-naphthalène), du perfluoro-(décahydrodiméthyl-naphthalène),
40 du perfluorodiméthyladamantane, du perfluoro-triméthylbicyclo[3.3.1]nonane, du perfluorotétrahydro-cyclopentadiène, du perfluorodicyclo[5.3.0]décane, du perfluorodiméthylbicyclo[3.3.1]nonane, ou un de leurs mélanges.

19. Trousse à médicaments selon la revendication 18, dans laquelle le perfluorocarbure est de la perfluoro-1-méthyldecaline.

45 20. Utilisation d'un perfluorocarbure visqueux, inerte, stable, transparent ou capable de transmettre la lumière, ou d'un dérivé de substitution de celui-ci pour la préparation d'un médicament pour utilisation extra-oculaire pour la lubrification, la protection ou le traitement de la surface de l'oeil.

21. Utilisation selon la revendication 20, dans laquelle le perfluorocarbure est un perfluorocyclo-carbure.

50 22. Utilisation selon la revendication 21, dans laquelle le perfluorocyclocarbure est du perfluoro-(méthylcyclohexane), du perfluoro-(1,3-diméthylcyclohexane), du perfluoro-(décahydro-naphthalène), du perfluoro-(décahydro-1-méthyl-naphthalène), du perfluoro-(décahydrodiméthyl-naphthalène), du perfluorodiméthyladamantane, du perfluoro-triméthylbicyclo[3.3.1]nonane, du perfluorotétrahydro-dicyclopentadiène, du perfluorodicyclo[5.3.0]décane, du perfluorodiméthylbicyclo[3.3.1]nonane, ou un de
55 leurs mélanges.

23. Utilisation selon la revendication 22, dans laquelle le perfluorocyclocarbure est de la perfluoro-1-méthyldecaline.

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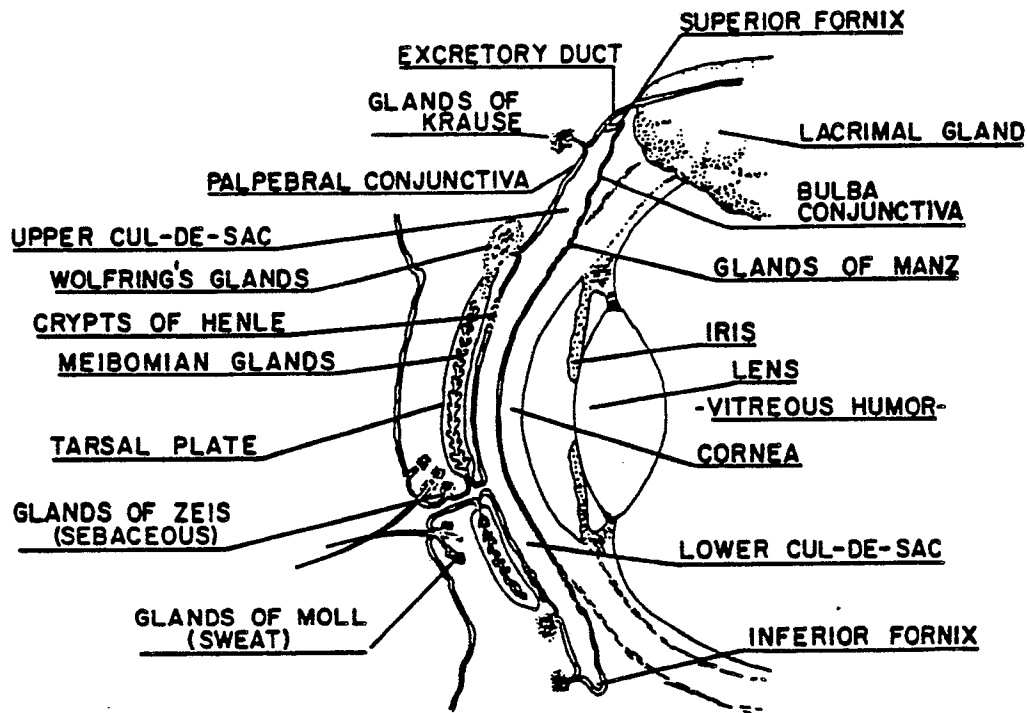


Fig. 1

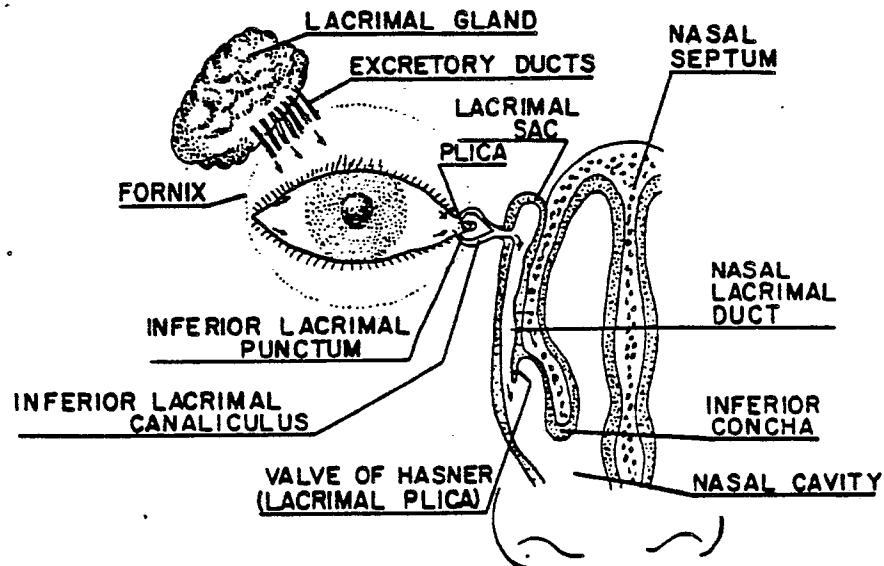


Fig. 2